

Fatigue

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Few clinical complaints can be as frustrating, yet be so common, as that of fatigue. It is estimated that close to 7 million office visits per year are generated for the complaint of fatigue. Further, it has been estimated that of the patients being seen by a primary care provider, up to 33% report fatigue as part of their symptom complex. Patients are often concerned that their fatigue results from a serious organic medical condition. A medical or psychiatric cause is identified in about two thirds of cases of chronic fatigue. In the majority of cases, which can be up to 80% in some studies, a psychiatric illness is found as the underlying cause. [Table 22-1](#) highlights the most common causes of fatigue.

As a clinical syndrome, fatigue generally refers to exhaustion during or after usual activities, or a lack of energy sufficient to begin these activities. Fatigue should be distinguished from weakness, shortness of breath, and hypersomnolence, which are possible markers for other disease processes, though these symptoms may coexist in a patient with fatigue.

Fatigue can be categorized based on the length of time the symptoms have been present. Recent fatigue represents symptoms presenting within 1 month; prolonged fatigue refers to symptoms lasting between 1 and 6 months; and chronic fatigue (not necessarily chronic fatigue syndrome, *per se*) refers to symptoms of greater than 6 months' duration.

This chapter presents the general approach to a patient with fatigue as a primary complaint, then focuses on the more common clinical syndromes associated with fatigue: anemia, cancer-related fatigue, depression, chronic fatigue and postviral fatigue, HIV, and hypothyroidism.

Symptoms

- Generalized tiredness and weakness +++++
- Depression (often) +++
- Lethargy with increased perceived sleep need

Signs

- Typically none in the setting of idiopathic fatigue with no underlying organic disorder

Workup

Fatigue is an extremely common complaint in primary care, though seldom is a serious organic cause identified. One large study found

Table 22-1. Common Causes of Fatigue

TYPE OF FATIGUE	CAUSES
Cardiopulmonary	Congestive heart failure Chronic obstructive pulmonary disease Aortic stenosis
Endocrine	Hypothyroidism Diabetes mellitus Hypercalcemia Chronic kidney disease Adrenal insufficiency
Infectious	Human immunodeficiency virus infection Tuberculosis Mononucleosis Hepatitis Cytomegalovirus
Medications	Hypnotics Antihypertensives Antidepressants
Neoplastic or hematologic	Occult malignancy Severe anemia Paraneoplastic syndrome
Psychologic	Depression Anxiety Somatization disorder
Rheumatologic	Rheumatoid arthritis Systemic lupus erythematosus Mixed connective tissue disease
Miscellaneous	Sleep apnea Idiopathic chronic fatigue Chronic fatigue syndrome

a prevalence of chronic fatigue, separate from a diagnosis of chronic fatigue syndrome, as between 1700 and 6300 cases per 100,000. Nonetheless, for patients with fatigue the consequences from a quality of life standpoint can be dire.

Patients with primary fatigue generally report being tired all the time, not particularly related to exertion and often not improved with rest. Conversely, patients with fatigue arising from organ-specific disease typically relate that they are unable to complete tasks due to increasing fatigue.

- Thorough history elucidating the specific tasks the patient is unable to perform as a measure of the degree of fatigue
- Investigation of other associated constitutional symptoms such as weight loss, night sweats, persistent fever, and thorough review of systems
- Assessment of psychiatric status through history and by use of an established depression inventory

- Thorough evaluation of prescription and nonprescription medications known to cause fatigue, most notably antihypertensives, hypnotics, antidepressants, neuroleptics, and drugs of abuse
- Physical examination should include: assessment for thyroid disease; full cardiopulmonary examination to detect evidence of CHF, valvular disease, or chronic lung disease; full neurologic examination including muscle strength, bulk, and tone; and examination of the lymphatic system to assess for lymphadenopathy.
- Laboratory studies are generally of low yield in the absence of abnormal findings in the patient history or on physical examination. However, it is reasonable to use laboratory tests to exclude other diseases. The Centers for Disease Control and Prevention (CDC) recommend as an accepted approach the following: CBC; serum chemistry including metabolic panel, creatinine kinase, hepatic function tests, and calcium; TSH; and ESR. Additionally, evaluation of iron studies, including serum ferritin, should be considered if indicated. Finally, targeted tests could include an HIV screen and a PPD based on history and risk profile.
- ECG, chest radiographs, and pulse oximetry are infrequently useful in the setting of a normal physical examination.

Comments and Treatment Considerations

Therapeutic goals for patients with fatigue are best focused on maintaining or reestablishing normal daily living patterns of personal and household duties, work-related activities, and personal relationships.

A prescription for regular exercise should be included in the plan. Maintenance of appropriate sleep hygiene must be emphasized (e.g., normal sleep-wake cycles, avoidance of inappropriate caffeine intake, intentional bedtime routine).

Suggest using an antidepressant agent, especially to patients exhibiting features of depression, but even those who do not may benefit. Consider treatment with oral iron replacement therapy, especially in women still menstruating and who have a low serum ferritin level.

ANEMIA

Anemia is a well-known cause of symptomatic fatigue and should be included in the assessment of the fatigued patient. Fatigue is especially prominent in the patient with a hematocrit of less than 30%, or someone that has a relatively acute anemia. Patients who experience a slowly developing anemia over time are often able to compensate and only in retrospect realize their degree of functional impairment due to fatigue. In patients with an identified anemia, correction of the anemia can lead to dramatic improvement in their fatigue (see Chapter 3 for a full discussion of the evaluation of and therapy for the anemic patient).

CANCER-RELATED FATIGUE

Although fatigue can be associated with the initial presentation of malignancy, fatigue alone as a presenting symptom of malignancy is unusual. Generally, other signs and symptoms, such as fever of unknown cause, diaphoresis, weight loss, respiratory symptoms, GI symptoms, or genitourinary symptoms will be present as well. In patients that do have fatigue as a primary presenting symptom of a malignancy, the cancer is far more likely to be hematologic as opposed to solid organ.

On the other hand, fatigue is extremely common among patients diagnosed with cancer and undergoing therapy, especially for those with metastatic disease. So common, in fact, that a separate clinical entity, known as cancer-related fatigue (CRF) has been defined as persistent tiredness or weakness that interferes with normal functioning, in the setting of known malignancy or cancer therapy. Fatigue is often reported by cancer patients to be one of the most difficult and distressing elements of their cancer and its treatment. CRF often results from many factors, most notably are anemia, chronic pain and pain therapy, emotional distress, poor sleep hygiene or disturbed sleep, poor nutrition (usually due to appetite loss or nausea), and other comorbid conditions. Additionally, disturbance of muscle metabolism and loss of muscle mass contribute to the weakness experienced by these patients. CRF can persist even after completion of the cancer therapy. Evaluation and management of these patients should focus on these potential reversible causes of fatigue.

Symptoms

- Generalized tiredness or weakness ++++
- Lethargy with diminished initiative
- Depression
- Organ-specific symptoms (chronic cough, hemoptysis, chronic dyspepsia)

Signs

- Anemia
- Neutropenia or leukocytosis
- Lymphadenopathy (often diffuse)
- Fever, often with diaphoresis, night sweats
- Unintended weight loss, with or without cachexia
- Organ-specific signs (i.e., hypoxia, hematuria, melena)

Workup

- In the setting of no known cancer:
 - Thorough history investigating associated constitutional symptoms (fever, weight loss, night sweats) and a careful, thorough review of organ systems
 - Physical and laboratory examination as discussed earlier in this chapter. Further evaluation is based on findings.

- In the setting of known cancer:
 - Assessment of severity of fatigue based on functional disability with ADLs
 - Assessment of stage of disease, type and phase of treatment, and response to treatment
 - Use of a standard fatigue inventory, such as the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)
 - Careful evaluation of sleep history, pain control and current treatment, and depression signs and symptoms
 - Nutritional assessment including both dietary intake and GI symptoms preventing proper eating (e.g., nausea, vomiting, loss of appetite, constipation)
- Thorough physical and laboratory evaluation, which may reveal anemia, kidney or hepatic disease (primary or as an effect of therapy), cardiopulmonary disease (primary or as an effect of therapy), or other comorbid condition

Comments and Treatment Considerations

Treatment of anemia has had the most profound effect on improvement in CRF. Various approaches, depending on the etiology of the anemia, include correction of ongoing blood loss; replacement of iron, vitamin B₁₂, and folate; transfusion of RBCs; and therapy with recombinant erythropoietin or darbepoetin. Target hemoglobin levels to maximize quality of life appear to be between 11 and 13 g/dL.

Other pharmacotherapy approaches for CRF have mixed results when assessed with placebo-controlled studies. Nonetheless, attempts have been made to alleviate symptoms with the psychostimulants methylphenidate, pemoline, and modafinil. These agents may be considered options in selected patients when no other option is available and in patients who experience sedation from opioid analgesics for pain control. Antidepressants are effective in patients with a strong depression component to their fatigue. Low-intensity, regular exercise is typically advised for patients with CRF after careful evaluation for contraindications (lytic bone lesions, thrombocytopenia). The effects of an exercise program appear to be maintenance of muscle mass, improved sleep, improved mental outlook, and improved functional capacity.

Sleep hygiene should be maintained as close to normal as possible. Typical counseling includes avoidance of caffeine, restful activities prior to nighttime sleep, avoidance of afternoon or evening naps, and keeping regular bedtime and wake times.

CHRONIC FATIGUE SYNDROME / POSTVIRAL FATIGUE

Two main subtypes of chronic fatigue have been identified: (1) chronic fatigue syndrome (CFS) and (2) idiopathic CFS or non-CFS. CFS is characterized by unexplained, persistent, or relapsing chronic fatigue, lasting 6 months or more, and ascribed associated

symptoms. In idiopathic chronic fatigue, the fatigue is significant but less severe and the associated symptoms may or may not be present. In both syndromes, the fatigue is not exertional, is not alleviated by rest, and results in substantial reduction in functioning. The diagnoses are controversial and complex. Potential etiologies discussed in the literature include infection, immune dysfunction, endocrine-metabolic dysfunction, neurally mediated hypotension, and psychologic distress. Fibromyalgia (FM) and TMJ disorder are generally considered allied conditions.

Contemporary North American literature considers CFS and postviral fatigue (PVF) as the same entity. British literature, however, using the term myalgic-encephalomyelitis considers PVF a distinct entity resulting from viral infection, most often Coxsackievirus or other enteroviruses. This is also separate from the short-term, self-limited fatigue that often accompanies acute viral infections (notably mononucleosis, cytomegalovirus, and hepatitis A and B). Often cited studies demonstrate enteroviral nucleic acid in muscle biopsies and unique enteroviral antigen in serum of up to 65% of patients with PVF. Other studies have shown evidence of Epstein-Barr virus in up to 20% of patients with PVF. Still other researchers have reported evidence that oxidative stress and excess free radical production from viral infection contribute to the chronic fatigue state. In animal studies, infection with one proposed etiologic agent, herpesvirus type I, resulted in significantly elevated F2-isoprostanes.

The CDC defines chronic fatigue syndrome as clinically evaluated, unexplained, persistent or relapsing fatigue with four or more associated symptoms, lasting 6 months or more. No physical findings were required to make the diagnosis. Fatigue, impairment in functioning, associated symptoms and psychological distress tend to be more severe in CFS patients. Psychological factors, primarily anxiety and depression, were present in a majority of CFS patients. Idiopathic chronic fatigue is associated with significant fatigue, but the symptoms are less severe than CFS and the prognosis is better.

The typical patient with CFS has a history of being a highly functional adult, varying in age from young to middle age (ages 20 to 55), who suddenly has significant impairment in functioning. Women are two times as likely to have the disease. The person may have a psychiatric history but she or he tends not to be someone with somatic complaints or who has chronic pain. The relative onset of the severe fatigue is often associated with a typical infection (e.g., a URI or true mononucleosis).

Patients with CFS have severe fatigue with four or more of the following symptoms:

Symptoms

- Substantial impairment of daily functioning* +++++
- Self-reported impairment in short-term memory or concentration*

*Symptoms included in the revised CDC criteria (1994) for CFS. Additional symptoms are described in the literature.

- Sore throat and/or muscle aches*
- Tender cervical or axillary lymph nodes*
- Migratory arthralgias without redness or swelling*
- Headaches of a new pattern or severity*
- Unrefreshing sleep*
- Postexertional malaise lasting 24 hours or more*
- Psychiatric problems
- Feverishness, rash, rapid pulse, chest pain, or night sweats
- Allergic rhinitis
- Abdominal cramps, weight changes

Signs

- Muscles are easily fatigued, but muscle strength is not affected.++++
- Excessive physical exercise exacerbates the symptoms.

Workup

CFS is a diagnosis of exclusion. Less than 10% of patients with chronic fatigue have CFS. The CDC and the International Chronic Fatigue Syndrome Study Group recommend the CFS workup to include (1) a thorough history and physical examination; (2) CBC with differential count; (3) ESR; (4) chemistry profile; (5) TSH; and other tests when clinically relevant. Screening tools for evaluating fatigue, anxiety, depression, degree of functional impairment, and illness beliefs may be useful in quantifying the symptom. The diagnosis is made if the patient has a typical history for CFS and no abnormality can be detected on physical examination or in the initial screening tests. Though *not* recommended, muscle biopsy and EMG are normal. Lymph nodes show only reactive hyperplasia if biopsied. Neuroimaging is not routinely performed.

Comments and Treatment Considerations

Beneficial treatments for chronic fatigue syndrome and idiopathic chronic fatigue are CBT and graded aerobic exercise programs. CBT focuses on altering beliefs and behaviors. Graded aerobic exercise programs prevent deconditioning and physical weakness. Both treatments improve scores on measures of fatigue, physical functioning, and quality of life.

Treatments with unknown effectiveness are antidepressants, corticosteroids, oral nicotinamide adenine dinucleotide, prolonged rest, yoga, coenzyme Q10, immunotherapy, dehydroepiandrosterone (DHEA), ginseng, vitamins, dietary supplements, and IM magnesium.

Antidepressants affecting both norepinephrine and serotonin (e.g., bupropion and sertraline) may be more effective than those acting predominantly on one neurochemical pathway. Citalopram (20 to 40 mg/day) when used for patients with idiopathic chronic fatigue, showed significantly and substantially reduced symptoms

* Symptoms included in the revised CDC criteria (1994) for CFS. Additional symptoms are described in the literature.

of fatigue, headaches, and muscle aches overall. Depression symptoms were not significantly lower in all subgroups.

Iron supplementation therapy may be beneficial in menstruating female patients with chronic fatigue, who have a baseline serum ferritin concentration less than or equal to 50 µg/mL.

DEPRESSION

In the setting of depression the symptom of fatigue is sustained, not resultant from physical exertion, and limits the patient's activities. Depression can occur by itself (unipolar) or as part of bipolar disorder. Three subtypes of unipolar depression are important to primary care physicians: (1) recurrent, major depressive disorder; (2) single-episode, major depressive disorder; and (3) dysthymia. See the chapter on depression for a full discussion of this topic.

Recurrent, major depressive disorder is the most common subtype seen in primary care and can be divided clinically into two groups: Atypical depression and typical depression. Fatigue tends to be the primary symptom of atypical depression, along with anxiety, anhedonia, and mood reactivity. Typical depression is characterized by dysphoria, tearfulness, low self-esteem, and appetite and sleep changes. Management for typical and atypical depression is generally the same.

Similarly, dysthymia is characterized as chronic, mild to moderate dysphoria, lasting 2 years or more. The vegetative symptoms (fatigue, appetite and weight changes, sleep disturbance, and psychomotor symptoms) in dysthymic individuals appear to be less common than in individuals experiencing a major depressive episode. Management for dysthymia and major depressive disorder is generally the same. Single-episode and recurrent major depressive disorders tend to have higher mortality risks than the dysthymia.

The DSM-IV criteria for the diagnosis of major depressive disorder, both single episode and recurrent, are at least 2 weeks of dysphoria or anhedonia accompanied by at least four additional symptoms of depression that cause significant distress and impairment of functioning.

Symptoms

- Anhedonia or dysphoria (with or without irritability) +++
- Fatigue, general tiredness, loss of energy or weakness +++
- Weight and/or appetite change (increase or decrease)
- Insomnia or hypersomnia ++
- Feelings of worthlessness, hopelessness, low self-esteem, and guilt
- Recurrent thoughts of death or suicidal ideation +
- Psychotic symptoms (hallucinations, delusions, cognitive distortions)

Signs

- Psychomotor retardation or agitation +++
- Diminished ability to think or concentrate, or indecisiveness ++

Workup

- See the chapter on depression for a thorough discussion of the workup.
- In general, limited laboratory testing (CBC, TSH, FSH) is recommended to rule out typical secondary medical causes. No laboratory findings are diagnostic of major depressive disorder or dysthymia.

Comments and Treatment Considerations

Up to 15% of individuals with severe major depressive disorder die by suicide. Monitor for suicidal ideation. Ask the patient about suicidal ideation, means, plan, and reason to live. Treatment for the depression may increase suicide risk.

Evaluate for manic symptoms and mixed episodes to rule out bipolar disorder, which is managed differently from unipolar depression. Watch for onset of depression after a death of a loved one or during the postpartum period. Up to 20% to 25% of individuals with specific medical conditions (e.g., diabetes mellitus, MI, carcinomas, stroke) will develop major depressive disorder during the course of their illness.

SSRIs, SNRIs, or DNRIs are the treatment of choice for mild and moderate depression. Fatigue, along with other physical symptoms, will often improve over the first month with SSRIs. Antidepressants that list fatigue as an adverse reaction are duloxetine, trazodone, and escitalopram oxalate. Watch for a gradual response of the antidepressants. Most take 4 to 6 weeks to show effects.

Some articles support psychotherapy and pharmacologic management as first-line therapy in moderately depressed patients. Some patients benefit from psychotherapy alone, others benefit from medication management alone. For mild to moderate depression, start with medication management and refer for a psychological evaluation and confirmation of the diagnosis.

The results of a randomized trial of 573 depressed patients in a primary care setting identified no differences in outcome measures between paroxetine, fluoxetine, and sertraline. A systematic review of 46 randomized controlled trials and 26 observational studies noted no significant differences in efficacy, tolerability, and outcome measures between second-generation antidepressants (SSRIs, venlafaxine, duloxetine, mirtazapine, and bupropion). For severe, refractory depression, referral to a psychiatrist is warranted and additional therapies such as antipsychotics, anticonvulsants, and ECT may be indicated.

HUMAN IMMUNODEFICIENCY VIRUS

Up to 60% of patients with HIV and up to 85% of patients with AIDS report moderate to severe fatigue as a problem in the course of their illness. Furthermore, HIV patients with fatigue were significantly more disabled than their nonfatigued counterparts across the whole spectrum of the SF-36 health survey. Overall quality of life was markedly affected by fatigue as a sole factor.

Historically, HIV-related fatigue has been assumed to correlate with stage of disease, relative CD4 count, and viral load. However, evidence has not found this to be the case. Rather, the strongest correlate of fatigue in the HIV-infected patient has repeatedly been shown to be the degree of psychologic distress and depression. Additionally, there does not seem to be a direct association between drug regimen and fatigue. Most HIV patients are treated with highly active antiretroviral therapy (HAART) combinations and although mortality from HIV has dramatically declined, neither the biologic response (decreased viral load, increased CD4 count) nor the taking of these medications seems to directly affect fatigue.

Interestingly, there is evidence that increased fatigue predicts lower adherence to medical therapy. Fatigue is identified as a primary reason for forgetting a dose, oversleeping and missing a dose, and/or resisting intensive medical therapy.

Symptoms

- Nonexertional fatigue, tiredness, general malaise +++
- Depression and anxiety ++
- Chronic pain, either organic from disease process or perceived
- Myalgias, arthralgias
- Sleep disturbance

Signs

- Positive HIV, with or without criteria for AIDS ++++
- Depression, as quantified by any validated depression rating scale
- Lymphadenopathy
- Weight loss and “wasting syndrome”
- Anemia, pancytopenia, or iron deficiency (usually nutritional)

Workup

- In general, no specific workup is required outside that already accomplished as part of the management of HIV infection.
- In the setting of new-onset fatigue in an HIV/AIDS patient, careful evaluation for depression should be done.
- Any additional psychiatric or neurologic signs or symptoms should prompt a more thorough neuropsychiatric evaluation, including neuroimaging as appropriate.

Comments and Treatment Considerations

There is a lack of good evidence regarding treatment of fatigue in the HIV-infected patient. All authors agree that in the patient with depression, standard therapy with antidepressant medications is warranted and generally effective. Additionally, there is growing evidence that CBT and regular graded exercise therapy are effective in treating medically unexplained fatigue and CFS. It is cautiously held that these results should be applicable to the HIV-infected population as well.

Of course, organic disorders such as anemia and iron deficiency should be treated by standard modalities. Finally, nutritional counseling should be considered for all HIV-infected patients, but

especially those suffering from fatigue would be well served with a structured dietary education program.

HYPOTHYROIDISM

Fatigue is a prominent presenting symptom of hypothyroidism. Most symptoms of hypothyroidism, such as fatigue, are nonspecific. The onset is often insidious and may be accompanied by other vague symptoms such as weakness, sluggishness, and weight gain. The symptoms of hypothyroidism derive from the deficit in circulating thyroid hormones and can be found in virtually all types of hypothyroidism regardless of the underlying etiology. The lack of thyroid hormones causes a generalized slowing of metabolic processes as well as the accumulation of matrix glycosaminoglycans in the interstitial spaces; either of these effects may induce fatigue depending on the involved organ. The organ systems most responsible for hypothyroidism-induced fatigue include the cardiovascular, respiratory, hematopoietic, and neurologic systems.

Thyroid hormones have both inotropic and chronotropic effects. A decrease in thyroid hormones results in decreased cardiac output at rest due to a reduction in contractility, stroke volume, and heart rate. Reduced cardiac output also contributes to decreased exercise capacity and relative shortness of breath during exercise, which may be perceived as fatigue.

Fatigue can result from impaired respiratory function as well as cardiovascular dysfunction. Although lung volumes usually remain unaffected, maximal breathing capacity and diffusing capacity are reduced due to hypoventilation from respiratory muscle weakness and reduced pulmonary responses to hypoxia and hypercapnia.

Decreased levels of thyroid hormones can also slow the production of erythropoietin resulting in a normocytic, normochromic anemia. In addition but less commonly, a pernicious (macrocytic) anemia may ensue due to atrophy of the gastric mucosa caused by antibodies found in about one third of patients with primary hypothyroidism.

Decreased cerebral blood flow, decreased glucose use, and a general depression of CNS function may cause patients to complain of fatigue and sluggish thought processes.

The clearance of many sedating drugs, including antiepileptics, hypnotics, and opioids is decreased in hypothyroidism. Drug toxicity may present as fatigue, even at minimal dosing.

Symptoms

- Fatigue, sluggishness, difficulty concentrating +++
- Heat or cold intolerance ++
- Constipation
- Peripheral paresthesias

Signs

- Periorbital puffiness, coarse dry skin, patchy hair loss
- Bradycardia, occasionally hypotension

- Slow relaxation phase of deep tendon reflexes
- Hypothermia

Workup

- Emphasis is placed on assessing the TSH level, with subsequent evaluation of the free T_4 and total T_3 levels.
- Further evaluation for Hashimoto's thyroiditis (including antithyroid antibody titer) and subacute thyroiditis (CBC, ESR) may be considered.
- Evaluation of any palpable abnormalities of the thyroid should also be performed via radioactive iodine uptake scanning or ultrasound (or both), or fine-needle biopsy as appropriate.

Comments and Treatment Considerations

Once the diagnosis of hypothyroidism is made, treatment is to replace the diminished circulating thyroid hormone. Levothyroxine is the most commonly used agent, but desiccated thyroid is available and preferred by some physicians and patients. Additionally, liothyronine (synthetic T_3) is at times used as an adjunct. HRT for hypothyroidism should be followed carefully with regular physician visits and serum levels of TSH, T_4 , and, when using liothyronine, T_3 to ensure maintenance in the therapeutic range.

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